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Letter to the Editor

High rate of reinfection with the SARS-CoV-2 Omicron variant

Dear Editor,

We read with interest that infection with Omicron variant can occur in patients who presented a high antibody titer, even though their concentration was at 2.4 higher than infection with Delta variant [1]. The SARS-CoV-2 pandemic has shown the succession or superposition of epidemics linked to numerous viral variants [2]. Until recently, the overall rate of reinfection with SARS-CoV-2 has been relatively low, below 2% according to several international studies [3, 4]. The Omicron (B.1.1.529) variant has been described for the first time on November 2021 in Gauteng province, South Africa and spread rapidly worldwide. One study conducted in South Africa demonstrated that it was associated with an increased hazard ratio of reinfection, suggesting its substantial ability to evade immunity from prior infection [5]. In addition, vaccine efficacy against this variant was reported to be reduced to around 56% for the Pfizer vaccine [6].

We report here the incidence and proportion of reinfections with the Omicron variant among patients diagnosed in our institute.

Our laboratory has massively screened SARS-CoV-2 infections by real-time reverse transcription-PCR (qPCR) under the same conditions since the emergence of this virus in France in February 2020. We thus have a cohort of patients screened and diagnosed as infected for the period February 27, 2020-March 6, 2022, making it possible to calculate the rate of reinfections over this entire period without the bias of variable screening strategy or capacity. An automatic reinfection detection system has been implemented through the laboratory information system of our institute's laboratory, on the basis of two qPCR-positive samples spaced at least 90 days apart with a negative qPCR between two episodes, according to the CDC definition of reinfection case [https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html]. SARS-CoV-2 RNA genotyping was performed by using sequencing or variant-specific qPCR, as described elsewhere [3].

From February 7, 2020 to March 6, 2022, 1646 of 80,863 patients found SARS-CoV-2-positive experienced a reinfection. Their mean age ± standard deviation at time of the second infection was 38.3 ± 16.4 years, ranging from 9 months to 97 years, and 60.1% were female. In Marseille, we observed five major epidemics of SARS-CoV-2 infections due to different mutants or variants (Fig. 1) [7]. The first epidemic from February to early June 2020 was driven by three mutants derived from the Wuhan-Hu-1 isolate that were classified into Nextstrain clades (Pangolin lineages) 20A (B.1), 20B (B.1.1) and 20C (B.1). The second epidemic from mid-June 2020 to February 2021 was due to multiple variants among which the 20A (B.1.416, a.k.a. Marseille-1 [7] variant, the 20A.EU2 (B.1.160, a.k.a Marseille-4) variant, the majority one, and the 20E.EU1 (B.1.117, a.k.a. Marseille-2) variant. The third epidemic during March 2021-June 2021 was mainly due to the Alpha (20I, B.1.1.7) variant. The Delta (B.1.617.2) variant was the one mostly responsible for the fourth epidemic that lasted from July 2021 to early November 2021. Finally, the fifth epidemic, due to the Omicron (B.1.1.529) variant, started in November 2021 and is still going on as of March 6, 2022.

Reinfection cases were observed since the second epidemic among patients whose first infection occurred during one of the five epidemics (Fig. 1). The overall mean time span between first infection and reinfection was 334 ± 146 days and significantly increased overtime from one epidemic to another (Supplementary Figure). The first patient reinfected with the Omicron variant was detected mid-December. Then, this variant rapidly became predominant in reinfected patients until the study's endpoint, as of 6 March 2022, with 885 cases out of 1397 (Fig. 1). In earlier studies, we reported that the prevalence of reinfection among SARS-CoV-2 infections diagnosed in our institute was 0.2% (58/29,154 cases), 0.3% (41/12,283 cases) and 1.5% (110/7152 cases) during the second, third and fourth epidemic (until 24 August 2021), respectively [3 ,8]. In the present study, we confirm a 1.5% reinfection rate (179/12,135 cases) during the entire fourth epidemic (until November 2021), and observe a marked increase in the reinfection rate that reaches 6.8% (1397/20,542 cases) during the on-going fifth epidemic (Fig. 2). Among 13,060 cases of first infections with the Omicron variant, 10,590 were due to the Omicron BA.1 variant (81.1%) and 2470 (18.9%) to the BA.2 variant. Among 885 cases of reinfection with the Omicron variant 834 (94.2%) were due to the BA.1 variant and 51 (5.8%) to the BA.2 variant. There were no cases of first infection with the BA.1 variant that were reinfected with the BA.2 variant.

Fig. 2 represents the prevalence of reinfection and the estimated risk for reinfection in SARS-CoV-2-infected patients according to the period of first infection. Contrary to our previous assessment that this estimated risk decreased over time [3], we observed little variation, between 2.4 and 3.0%, in this updated study. This is likely because of cumulative numbers of reinfections overtime with occurrence of new cases of reinfection that were diagnosed after our previous assessment.

The increase in the proportion of reinfections with the Omicron variant is additional evidence that the genetic variability of SARS-CoV-2 has resulted in antigenic changes leading to reduced protection conferred by a previous infection. Our recent observations of a lower severity of infections with the Omicron variants as indicated by low rates of hospitalization, transfer to intensive care units, and death is good news in this context [9, 10]. The Omicron variant is likely distantly related to other SARS-CoV-2 variants which may account for a higher rate on reinfection and lower efficacy of vaccines. Indeed, despite the currently considerable proportions of people vaccinated and/or infected in France, present data

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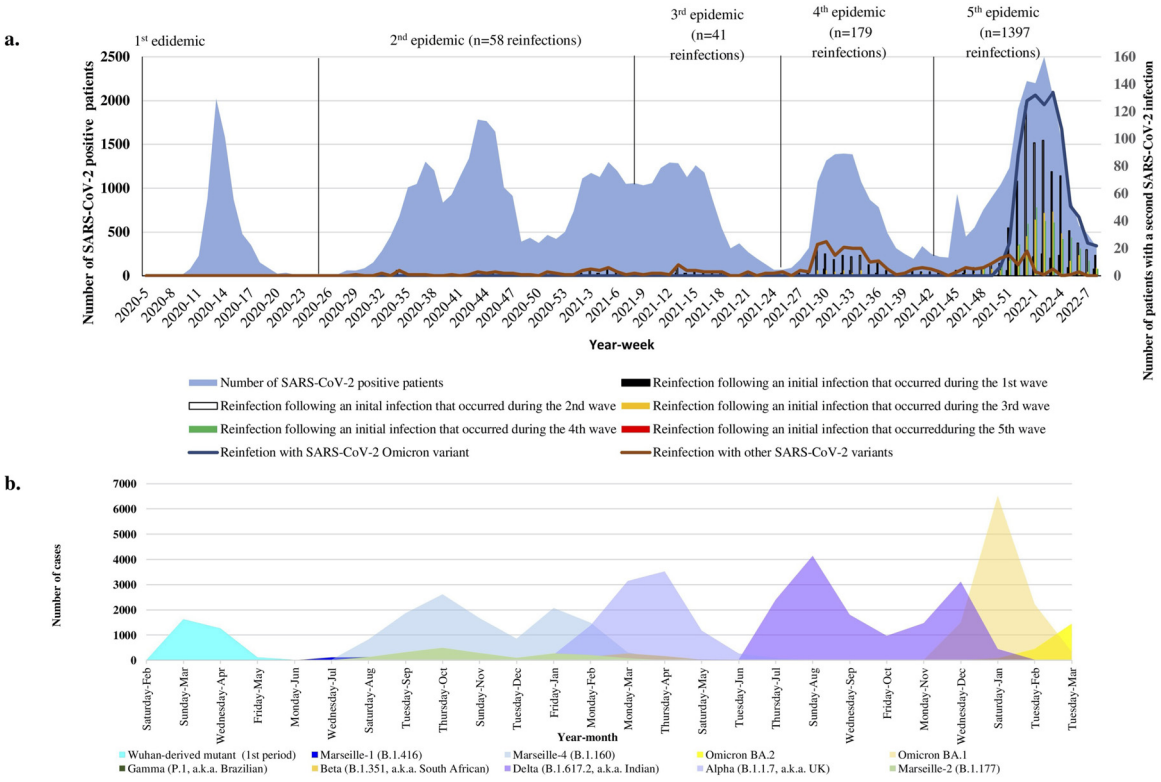

Fig. 1. Dynamics of SARS-CoV-2 infections (left axis) and reinfections (right axis) (a) and of major SARS-CoV-2 variants determined (b) in patients diagnosed at IHU Méditerranée Infection, 2020–2022.

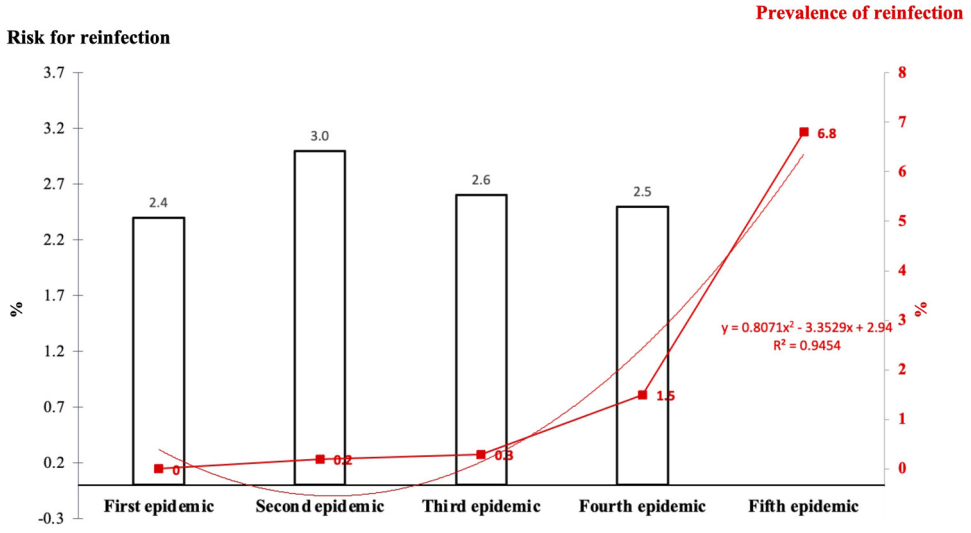

Fig. 2. Frequency of reinfection (proportion of infected patients during a given epidemic who had previous infection with SARS-CoV-2, red curve) and estimated risk for reinfection (proportion of patients first infected during a given epidemic who get reinfected at the time the study.

and recently published data [5] suggest that resulting immunity could not prevent an endemicization of SARS-CoV-2.

Author contributions

Conceptualization: Didier Raoult and Philippe Gautret; Investigation: Philippe Colson, Linda Houhamdi, Didier Stoupan and Nhu Ngoc Nguyen; Formal analysis: Van Thuan Hoang and Nhu Ngoc Nguyen; Writing original draft: Philippe Gautret, Philippe Colson and Nhu Ngoc Nguyen; reviewing and editing: Philippe Gautret, Philippe Colson and Didier Raoult. All authors have contributed to this study and approved the final version of the manuscript and its revision.

Ethical approval

This retrospective study has been approved by the ethics committee of the University Hospital Institute Méditerranée Infection (No. 2022–016). Access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of Assistance Publique-Hôpitaux de Marseille (APHM) and was recorded in the European General Data Protection Regulation registry under number RGPD/APHM 2019–73

Supplementary Material

Supplementary Figure. Mean time (days) between first infection and reinfection according to time when reinfection occured.

Declaration of interest

The authors have no conflicts of interest to declare relative to the present study. Didier Raoult was a consultant for the Hitachi High-Technologies Corporation, Tokyo, Japan from 2018 to 2020. He is a scientific board member of the Eurofins company and a founder of a microbial culture company (Culture Top). Funding sources had no role in the design and con-duct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, or approval of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.04.034.

CRediT authorship contribution statement

Nhu Ngoc Nguyen: Investigation, Formal analysis, Writing – original draft. **Linda Houhamdi:** Investigation. **Van Thuan Hoang:** Formal analysis. **Didier Stoupan:** Investigation. **Didier Raoult:** Conceptualization, Writing – review & editing. **Philippe Colson:** Investigation, Writing – original draft, Writing – review & editing. **Philippe Gautret:** Conceptualization, Writing – original draft, Writing – review & editing.

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Nhu Ngoc Nguyen, Linda Houhamdi
Aix Marseille University, IRD, AP-HM, SSA, VITROME, Marseille, France
IHU-Méditerranée Infection, Marseille, France

Van Thuan Hoang
Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam

Didier Stoupan
IHU-Méditerranée Infection, Marseille, France

Pierre-Edouard Fournier
Aix Marseille University, IRD, AP-HM, SSA, VITROME, Marseille, France
IHU-Méditerranée Infection, Marseille, France

Didier Raoult, Philippe Colson
Aix-Marseille University, IRD, AP-HM, MEPHI, Marseille, France
IHU-Méditerranée Infection, Marseille, France

Philippe Gautret*
Aix Marseille University, IRD, AP-HM, SSA, VITROME, Marseille, France
IHU-Méditerranée Infection, Marseille, France

*Corresponding author: Philippe Gautret, VITROME, Institut Hospitalo-Universitaire Méditerranée Infection, 19-21 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France.
E-mail address: philippe.gautret@club-internet.fr (P. Gautret)